

REMARKS

Applicants thank the Examiner for the thorough examination given the present application.

Status of the Claims

Claims 8-10 and 12-14 will be pending in the above-identified application upon entry of the present amendment. Claim 8 has been amended. Claims 12-14 have been added. Support for the recitations in claim 8 and for new claims 12-14 can be found in claims 7 and 9-10 as well as in the publication of the present specification, *inter alia*, at paragraphs [0049]-[0050] and [0054]-[0055]. Thus, no new matter has been added. Based upon the above considerations, entry of the present amendment is respectfully requested.

In view of the following remarks, Applicants respectfully request that the Examiner withdraw all rejections and allow the currently pending claims.

Statement of the Substance of the Interview

Applicants would like to thank the Examiner for her time during the interview on March 16, 2011. Applicants appreciate the courtesies extended to them in this application. Based on the discussions during the interview, Applicants believe that the claims are now in condition for allowance. Should the Examiner believe that there remains any outstanding issues, Applicants respectfully request that the Examiner contact Applicants' Representative so as to expedite resolution of these outstanding issues, via an Examiner's Amendment or the like.

Information Disclosure Citation

Applicants thank the Examiner for considering the references supplied with the Information Disclosure Statement filed September 20, 2010 and for providing Applicants with an initialed copy of the PTO-SB08 form filed therewith.

Drawings

Since no objection has been received, Applicants assume that the drawings are acceptable and that no further action is necessary. Confirmation thereof is respectfully requested.

Issues under 35 U.S.C. § 103(a)

1) Claims 1, 4, 6, and 8-9 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Josephson et al. '029 (US 2003/0092029) in view of Rohr '970 (US 5,445,970) and further in view of Thompson '304 (US 2003/0190304).

2) Claims 5, 7, and 10 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Josephson et al. '029 in view of Rohr '970 and Thompson '304 and further in view of Foster '879 (US 4,444,879).

Applicants respectfully traverse. Reconsideration and withdrawal of these rejections are respectfully requested based on the following considerations.

Legal Standard for Determining Prima Facie Obviousness

MPEP 2141 sets forth the guidelines in determining obviousness. First, the Examiner has to take into account the factual inquiries set forth in *Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), which has provided the controlling framework for an obviousness analysis. The four *Graham* factors are:

- (a) determining the scope and content of the prior art;
- (b) ascertaining the differences between the prior art and the claims in issue;
- (c) resolving the level of ordinary skill in the pertinent art; and
- (d) evaluating any evidence of secondary considerations.

Graham v. John Deere, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966).

Second, the Examiner has to provide some rationale for determining obviousness. MPEP 2143 sets forth some rationales that were established in the recent decision of *KSR International Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

As the MPEP directs, all claim limitations must be considered in view of the cited prior art in order to establish a *prima facie* case of obviousness. See MPEP 2143.03.

The Present Invention

In the conventional art, magnetic beads having a large diameter have been utilized in the separation and refinement of biological materials using an antigen-antibody binding. Magnetic beads having a small diameter have been utilized in the detection of antigen (see, e.g., Josephson et al. '029).

However, since the magnetic signal output provided by magnetic beads having a small diameter is weak, the high-sensitivity detection cannot be provided by the magnetic beads having a small diameter. Since magnetic signal output depends on the volume of a magnetic bead, the magnetic signal output increases in proportion to the cube of the diameter of the magnetic bead.

In contrast, the movement of magnetic beads having a large diameter is low, and the speed of the antigen-antibody reaction is slow. In other words, the reaction percentage after a lapse of a predetermined time is small. As a result, high-sensitivity detection cannot be provided (see paragraph [0002] of the publication of the present application).

When the magnetic bead has a large diameter of 0.5 to 10 μm , high-sensitivity detection can be provided by coupling the antibody to it via the spacer of polyalkylene glycol having 50 to 500 units because of an improvement of the movement of the antibody portion. Specifically, in the present invention, the sandwich structure is formed by sandwiching the antigen between the specific primary antibody immobilized on the substrate material and the specific movable secondary antibody labeled by the magnetic beads having the above large diameter. The sandwiched antigen is detected by the magnetic signal from the magnetic labeling of the above secondary antibody constituting this sandwich structure. The above secondary antibody labeled by the magnetic beads constituting this sandwich structure can provide both effects of the high reaction of the antigen and the strong magnetic signal. Thus, both effects of the strong magnetic signal output and the high speed of the antigen-antibody reaction can be provided according to the present invention. As a result, high-sensitivity detection can be achieved. Thus, the present invention achieves several advantageous effects.

Distinctions over the Cited References

Josephson et al. '029 disclose that the nanoparticles have an overall size of less than 1-100 nm and that the metal oxides are crystals of 1-25 nm (paragraph [0063]). Additionally, Josephson et al. '029 disclose that the overall size of the nanoparticles is 15 to 200 nm when the polymer coating is conducted.

Josephson et al. '029 also recite, "In all embodiments, the nanoparticles are attached (linked) to the binding moieties via functional groups. In some embodiments, the nanoparticles are associated with a polymer that includes the functional groups, and also serves to keep the metal oxides dispersed from each other" (paragraph [0061]).

However, the polymer disclosed in Josephson et al. '029 is used as a coating agent to coat the surfaces of the nanoparticles (paragraph [0063]). In other words, the polymer of Josephson et al. '029 is not used as a spacer. Additionally, Josephson et al. '029 fail to teach or suggest any spacer.

In contrast, the present invention requires a spacer of polyalkylene glycol (e.g., PEG) having 50 to 500 repeat units. This polyalkylene glycol spacer acts to improve the reaction by distancing the binding moiety from the nanoparticle (which is referred to as "the magnetic bead" in the present specification). However, in the case of using polyalkylene glycol for the coating of the nanoparticle, such an action cannot be physically provided because the outer surface is only expanded. Under such circumstances, the replacement of the coating polymer disclosed in Josephson et al. '029 by a spacer, which is functionally different from a coating agent, would not be obvious to one of ordinary skill in the art.

Additionally, the conjugates in Josephson et al. '029 are divided into three groups: the monodispersed nanoparticles having 4-100 nm in size, the aggregates which are composed of 2-20 nanoparticles and have 100-500 nm in size, and the aggregates which contain greater than 20 nanoparticles and have greater than 500 nm in size (paragraphs [0132]-[0134]). Regarding the third group of the aggregates which contain greater than 20 nanoparticles and have greater than 500 nm in size, Josephson et al. '029 clearly disclose, "The cluster is not useful since it typically clumps and falls out of solution" (paragraph [0134]; emphasis added). This recitation indicates that Josephson et al. '029 excludes the nanoparticles having greater than 500 nm in size. In other words, this recitation indicates that Josephson et al. '029 teach away from "a magnetic bead having a diameter of 0.5 to 10 μm " recited in the present invention.

Thus, Josephson et al. '029 only disclose the conjugates formed by binding a magnetic particle and a binding moiety via a functional group of a polymer, wherein the magnetic particle is produced by the polymer coating of a metal oxide having 1-25 nm in size. In short, as described above, the replacement of the coating polymer disclosed in Josephson et al. '029 by a spacer, which is functionally different from a coating agent, would not be obvious to one of ordinary skill in the art. Additionally, Josephson et al. '029 teach away from "a magnetic bead having a diameter of 0.5 to 10 μm " recited in the present invention. Rohr '970, Thompson '304, and Foster '879 fail to overcome these deficiencies.

The Examiner relies on Thompson '304 to disclose binding two polypeptides with a PEG spacer. However, the PEG spacer disclosed in Thompson '304 is not used to couple the magnetic bead labeled particle to the binding moiety. Additionally, Thompson '304 fails to teach or suggest that the PEG spacer is used in order to couple the magnetic bead labeled particle to the binding moiety. Therefore, Thompson '304 fails to teach or suggest the specific spacer required in the present invention.

Furthermore, as described above, claim 8 recites the following features: (a) "binding the antigen to an immobilized primary antibody to form a conjugate on a detection area of an adsorbing substrate," (b) "binding the antigen to a labeled secondary antibody to form a sandwich structure conjugate," (c) "washing away unreacted labeled secondary antibody," and (d) "detecting a magnetic signal from the sandwich structure conjugate to detect the antigen,"

However, Josephson et al. '029 fail to teach or suggest at least the above feature (a) or "the sandwich structure" recited in the above feature (b).

To establish a *prima facie* case of obviousness of a claimed invention, all of the claim limitations must be disclosed by the cited references. As discussed above, Josephson et al. '029 in view of Rohr '970 and Thompson '304, with or without Foster '879, fail to disclose all of the claim limitations of independent claim 8, and those claims dependent thereon. Accordingly, the combination of references does not render the present invention obvious.

Furthermore, the cited references or the knowledge in the art provide no reason or rationale that would allow one of ordinary skill in the art to arrive at the present invention as claimed. Therefore, a *prima facie* case of obviousness has not been established, and withdrawal of the outstanding rejections is respectfully requested. Any contentions of the USPTO to the contrary must be reconsidered at present.

Should the Examiner assert that the present invention is still obvious over the cited references, Applicants respectfully submit that the present invention achieves unexpectedly superior results, which rebuts any *prima facie* case of obviousness. Specifically, independent claims 8 and 12 recite that "the spacer is polyalkylene glycol having 50 to 500 repeat units." The present specification states:

While spacers of various lengths may be used in the present invention, spacers have a specific length of preferably 10 Å to 2000 Å, more preferably 200 Å to 2000 Å in order to produce a higher effect. Such a length can be obtained by, for example, in the case of polyalkylene glycol (hereinafter may be abbreviated as PALG), a structure in which 2 to 500, particularly 50 to 500, PALG monomers are repeated. When polyethylene glycol (hereinafter PEG) is used as polyalkylene glycol, the length can be obtained when polyethylene glycol has a weight average molecular weight of 2200 to 22000, preferably approximately 3000 within 2500 to 4000 (paragraph [0015]).

In other words, the weight average molecular weight of the polyalkylene glycol is related to its length.

In this regard, Example 3 of the present specification provides an example using a PEG-attached secondary antibody 1 compared with a PEG-attached secondary antibody 2 wherein the PEG has a lower molecular weight. As shown in Tables 3-4 (reproduced below), the PEG-attached secondary antibody 1 provides unexpectedly superior results over PEG-attached secondary antibody 2. As the Examiner admits, Josephson et al. '029 do not disclose a "polyalkylene glycol having 50 to 500 repeat units." Thus, PEG-attached secondary antibody 2 strongly evidences that the cited references do not produce the results of the present invention since the criticality of a "polyalkylene glycol having 50 to 500 repeat units" has been proven.

[Table 3]

Beads used	Conditions of labeling of secondary antibody with magnetic beads	Purified antigen concentration antigen: ribosomal protein L7/L12 of <i>Mycoplasma pneumoniae</i>			
		100 ng/ml	10 ng/ml	1 ng/ml	Negative sample
Dynabeads MyOne Streptavidin	Magnetic bead-labeled, PEG-attached secondary antibody 1	O	O	O	×
	Magnetic bead-labeled, PEG-attached secondary antibody 2	O	O	×	×
	Magnetic bead labeled secondary antibody 3 (no PEG)	O	O	×	×

In the table, "O" means that magnetic beads were observed in the CCD camera observation.

"×" means that magnetic beads were not observed in the CCD camera observation.

[Table 4]

Beads used	Conditions of labeling of secondary antibody with magnetic beads	Purified antigen concentration antigen: ribosomal protein L7/L12 of <i>Mycoplasma pneumoniae</i>			
		100 ng/ml	10 ng/ml	1 ng/ml	Negative sample
Dynabeads MyOne Streptavidin	Magnetic bead-labeled, PEG-attached secondary antibody 1	601 mV	83 mV	52 mV	below detection limit
	Magnetic bead-labeled, PEG-attached secondary antibody 2	337 mV	55 mV	below detection limit	below detection limit
	Magnetic bead labeled secondary antibody 3 (no PEG)	462 mV	57 mV	below detection limit	below detection limit

Relevant to these § 103(a) rejections, *Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966) has provided the controlling framework for an obviousness analysis, wherein a proper analysis under § 103(a) requires consideration of the four *Graham* factors. One such factor includes the evaluation of any evidence of secondary considerations (e.g., commercial success; unexpected results). 383 U.S. at 17, 148 USPQ at 467. In this regard, Applicants respectfully submit that the present invention has achieved unexpected results, whereby such results rebut any asserted *prima facie* case of obviousness. See *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). Also, the comparative showing need not compare the claimed invention with all of the cited prior art, but only with the closest prior art. See MPEP 716.02(b) and 716.02(e).

According to MPEP 2145, rebuttal evidence and arguments can be presented in the specification, *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995). Office personnel should consider all rebuttal arguments and evidence presented by Applicants. See, e.g., *Soni*, 54 F.3d at 750, 34 USPQ2d at 1687 (error not to consider evidence presented in the specification). Rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. Rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties. *In re Dillon*, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990).

As stated in *KSR International Co. v Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007), “rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” Furthermore, the mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *Id.* As described above, Applicants have shown that the present invention achieves unexpected and unpredictable results. Thus, due to the unexpected results as achieved by the present invention, the rejections have been overcome. Reconsideration and withdrawal of these rejections are respectfully requested. Any contentions of the USPTO to the contrary must be reconsidered at present.

With respect to the above evidence of unexpected results, the Examiner argues that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. Applicants agree. However, in this case, Applicants are not showing nonobviousness. Rather, the unexpected results rebut any asserted *prima facie* case of obviousness. Specifically, the present invention only needs to be compared with the closest prior art and not a combination of references (see MPEP 716.02(e)(III)). Thus, the Examiner should consider the evidence of unexpected results as it relates to Josephson et al. ‘029, the closest prior art. Thus, due to the unexpected results as achieved by the present invention, the rejections have been overcome.

New Claims 12-14

Claims 12-14 have been added for the Examiner’s consideration. Applicants respectfully submit that claims 12-14 are allowable for the reasons given above. In addition, claims 12-14 recite further limitations which are not disclosed or made obvious by the cited references. For example, claim 12 recites (e) “a primary antibody immobilized on a detection area of an adsorbing substrate” and (f) “a reagent containing a magnetic bead labeled secondary antibody in a bead concentration of 0.01% to 1%.” Josephson et al. ‘029 and the other cited references fail to disclose at least the above feature (e).

Conclusion

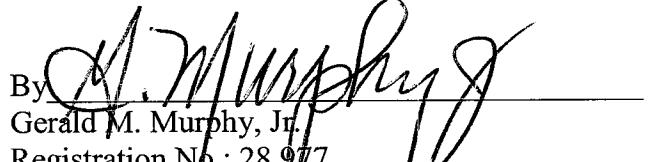
All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action, and as such, the present application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Chad M. Rink, Registration No. 58,258, at the telephone number of the undersigned below to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Director is hereby authorized in this, concurrent, and future replies to charge any fees required during the pendency of the above-identified application or credit any overpayment to Deposit Account No. 02-2448.

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Respectfully submitted,

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